## REMARKS

The amendment to the title finds support in the specification and claims as originally filed, for example, at page 8, lines 1-2. The amendment to the specification updating the priority claim adds the U.S. patent number corresponding to the application named in the specification as filed.

The amendment inserting the phrase "the clinical manifestations of" into Claim 1 finds support in the specification, for example, at page 8, lines 1-2; page 11, lines 23-35; page 12, lines 1-3; and elsewhere in the specification and claims as originally filed. For example, "disorders characterized by dysregulation of the GH/IGF axis in a mammal" are described as showing "clinical manifestations of either IGF excess or deficiency and/or GH resistance and/or deficiency, the latter being manifested by reduced levels of IGFBP-3 and/or increased levels of IGFBP-1" (page 11, lines 26-27).

The amendments to claims 1 and 2 inserting definitions of the acronyms used in the claims find support in the specification, for example, at page 1, lines 15 and 26; at page 10, lines 20-34 and page 25, line 11. The amendment to Claim 4 removes superfluous spaces. The amendment to Claim 5 finds support in the specification, for example, at page 26, lines 1-13. The amendments to Claim 7 find support in the specification, for example, at page 13, lines 28-31.

No new matter is added by way of the amendments.

Claims 1-14 are pending in the application. Claims 8-14 stand withdrawn pursuant to a Restriction Requirement made Final in the Office Action mailed July 18, 2003. Claims 1-7 stand rejected under 35 U.S.C. §112, first paragraph as allegedly claiming subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 1-7 also stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Applicants respectfully traverse these rejections.

The specification stands objected to for informalities: for not stating the updated status of the parent non-provisional application; for having a title that is allegedly not descriptive; and for having numerous spaces before the term "chronic" in Claim 4. As discussed below, applicants believe these objections to be overcome by the instant arguments and amendments.

**The Rejections to Claims 1-7 under 35 U.S.C. §112, first paragraph**

Claims 1-7 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly claiming subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The amount of disclosure required to be supplied by an enabling specification has been discussed and defined in court decisions. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also* Amgen Inc. v. Chugai Pharms. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991).

A specification need not provide exhaustive detail or description. "Enablement is not precluded by the necessity for some experimentation ... [the] experimentation needed to practice the invention must not be undue experimentation." Enzo Biochem, Inc. v. Calgene, Inc. 188 F.3d 1362, 1371 (Fed. Cir. 1999).

Claims 1-7 recite methods for treating the clinical manifestations of a disorder characterized by dysregulation of the GH/IGF axis in a mammal. Disorders characterized by dysregulation of the GH/IGF axis in a mammal are disclosed in the specification as being "characterized by defects in growth, physiology, and/or glycemic control" (page 11, lines 25-26) and with "clinical manifestations of either IGF excess or deficiency and/or GH resistance and/or deficiency, the latter being manifested by reduced levels of IGFBP-3 and/or increased levels of IGFBP-1" (page 11, lines 26-27). Most such disease states are characterized by a common biochemical profile as disclosed in the specification at page 4, lines 29-35 and page 12, lines 4-12. Thus, as

disclosed in the specification, diseases characterized by dysregulation of the GH/IGF axis share common defects, common clinical manifestations, and a common biochemical profile that make it possible to treat such clinical manifestations by the IGF-I variants of the invention.

Treating a disorder is disclosed as including both "therapeutic treatment and prophylactic or preventative measures" (page 13, lines 17-18). Use of the peptides of the invention in treating such disorders is discussed in the specification, for example, at page 8, lines 1-4; page 25, line 13 to page 26, line 17; page 42, line 13 to page 43, line 13. Methods of treatment are described in the specification, for example, at page 11, lines 23-35; page 12, lines 1-3; page 21, line 26 to page 22, line 10. Dosages to be delivered are discussed, for example, at page 22, line 11 to page 23, line 19.

Such treatments are also discussed elsewhere in the specification. Applicants note that, on pages 3 and 4 of the present Office Action, the Examiner has listed some of the teachings related to the claimed methods that are provided by the specification: the accumulation of active IGF molecules in the kidney could be beneficial in chronic or acute renal failure; that these conditions are characterized by abnormally high levels of IGFBP-1 and IGFBP-2; that these conditions are characterized by a reduction of IGF-I synthesis; IGF-I variants have been radiolabeled and administered to mammals, and that the majority of radiolabeled IGF molecules are detected in the kidney; and that IGF-I variants are cleared faster from the blood of a mammal than the wild-type.

However, although noting this disclosure, the Examiner states that "the specification does not teach treating a disorder characterized dysregulation of the GH/IGF axis in a mammal by administration of any IGF-I variant" (page 4, lines 14-15 of the present Office Action) and that "[u]ndue experimentation would be required ... to determine the optimal quantity, duration, and route of administration of an IGF-I variant...." (page 4, lines 15-17).

Applicants respectfully disagree, and submit that the specification provides disclosure sufficient to teach one of ordinary skill in the art how to practice the claimed invention. In particular, Example 3, entitled "Treatment of Humans" discloses how a peptide of the invention may be used to bind to a IGFBP and thus to displace

endogenous IGFs. Such binding to a IGFBP and displacement of endogenous IGFs would affect the amount of circulating IGF and is an example of treatment of a clinical manifestation of a disorder characterized by dysregulation of the GH/IGF axis in a mammal. A disorder characterized by dysregulation of the GH/IGF axis in a mammal may be treated, for example, by affecting IGF-I binding to IGFBP and by affecting the amount of circulating IGF, as indicated, for example, at page 13, lines 12-14; page 25, lines 13-4 and 28-29; and page 26, lines 1-2.

In addition to this example and to the teachings discussed by the Examiner, applicants respectfully note that the specification provides a significant amount of disclosure describing how to practice the invention. For example, further disclosure related to **treatment methods** may be found, for example, at pages 21 –26. **Modes and methods of administration** are discussed, for example, at page 21, lines 26-33; page 23, lines 20-32; page 25, lines 4-34 and page 26, lines 1-13. **Formulation of pharmaceutical compositions** including IGF-I variants are discussed, for example, at page 24, lines 1-35. **Dosages** and **methods of determining effective dosages** are discussed, for example, at page 22, lines 11-32, detailing what is, and how to determine, an effective amount of an IGF-I variant. **Treatment regimens** are discussed, for example, at page 23, lines 13-17. Other particulars regarding **alternative delivery methods** (*e.g.,* page 23, lines 20-34) and **modes of preparation and storage** (*e.g.,* page 24, lines 30-35 and page 25, lines 1-3) are also disclosed in the specification.

A method for evaluating the amount of disclosure that is required of an enabling specification is described in *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). In this case, the Federal Circuit set forth a number of factors that may be considered in making a determination as to whether a disclosure would require undue experimentation to enable an invention. The *Wands* factors include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the

claims.

It should be noted that the *Wands* factors are illustrative, not mandatory and "[w]hat is relevant depends on the facts." Enzo Biochem, Inc. v. Calgene, Inc. 188 F.3d 1362, 1371 (Fed. Cir. 1999).

Applicants respectfully submit that the quantity of experimentation (*Wands* factor 1) required in order to determine the parameters for the treatment methods claimed in the application (*e.g.,* dosages, dosing regimen, etc.) as described in the specification (for example, at page 21, lines 26-33; page 22, lines 11-32; page 23, lines 13-17; and page 24, lines 1-35) is not large, and consists of experiments that are routine in the art.

Applicants respectfully submit that the amount of direction or guidance provided by the specification (*Wands* factor 2) is considerable, as discussed above. Such direction and guidance is reviewed above; as an indication of the amount of direction and guidance provided, applicants reiterate that the specification discusses **treatment methods** (*e.g.,* at pages 21 –26); **modes and methods of administration** (*e.g.,* at pages 21, 23, 25, and 26); **pharmaceutical formulations** including IGF-I variants (*e.g.,* at page 24); **dosages** and **methods of determining effective dosages** (*e.g.,* at page 22); **treatment regimens** (*e.g.,* at page 23).

With respect to *Wands* factor 3, applicants respectfully note that the specification includes working examples (*e.g.,* Example 3, "Treatment of Humans," Example 2, and other data). The nature of the invention (*Wands* factor 4), and the state of the clinical and pharmaceutical arts at the time of the invention (*Wands* factor 5), are such that the methods for using the animal data and human protocols presented in the specification may be routinely applied to provide the claimed methods.

The relative skill in the pharmaceutical and medical arts (*Wands* factor 6) is high, requiring less disclosure in order to teach one of ordinary skill in the art than might be true for other arts. The predictability or unpredictability of the art (*Wands* factor 7) is moderate, since although biological research may be unpredictable a the outset, the state of the art as regards the clinical manifestations of disorders characterized by dysregulation of the GH/IGF axis in a mammal is well advanced. This may be seen by the extensive literature in the field (see, *e.g.,* the citations at pages 1-7) and by the well-

characterized clinical and biochemical profiles of the clinical manifestations of such disorders (see, *e.g.*, the literature cited on pages 1-7, and particularly the discussion on page 4, lines 29-35; page 11, lines 26-27; and page12, lines 4-12).

The breadth of the claims (*Wands* factor 8) is small, given that the claims are directed specifically to a method of treating "the clinical manifestations of a disorder characterized by dysregulation of the GH/IGF axis in a mammal." Thus, the claimed methods relate only to such manifestations, and only in mammals. The claimed methods are further limited in that the claimed methods require that the treatment comprise administration of "an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a glycine, or a serine residue." Such a treatment methods are thus limited to such clearly defined compounds. Accordingly, applicants submit that the breadth of the claims is small.

Taking all the *Wands* factors into account, applicants respectfully submit the specification provides an enabling disclosure, including extensive and detailed disclosure pertaining to methods for treating the clinical manifestations of disorders characterized by dysregulation of the GH/IGF axis in a mammal. Accordingly, applicants believe the rejections of Claims 1-7 under 35 U.S.C. §112, first paragraph, are overcome.

**The Rejections to Claims 1-7 under 35 U.S.C. §112, second paragraph**

Claims 1-7 stand rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Applicants respectfully traverse this rejection.

The Examiner states that the acronyms IGF-I, GH/IGF and IGFBP-1 render the claims indefinite. Having spelled out these abbreviations in the claims, Applicants respectfully submit that this ground of rejection is overcome.

The Examiner states that the term "renally-active molecule is a relative term which renders the claim indefinite," suggesting that the degree of activity and type of molecule are undefined in the claim. However, as noted by the Examiner, a definition

of the term "renally-active molecule" is provided in the specification (*e.g.*, at page 13, lines 15-16). In addition, examples of such molecules are provided, *e.g.*, at page 26, lines 1-13. As amended, claim 5 defines the types and activity of the renally-active molecules of the claim. Accordingly, Applicants respectfully submit that this ground of rejection is overcome.

The Examiner states that the limitation "both amino acid residues of the variant" has insufficient antecedent basis. Having amended the claim to recite the antecedent basis from Claim 1, applicants respectfully submit that this ground of rejection is overcome.

Accordingly, Applicants respectfully submit that the rejections to Claims 1-7 under 35 U.S.C. §112, second paragraph are overcome.

**The Objections to the Specification**

The section of the specification entitled "Related Applications" was objected to as not being updated to include the serial number of the U.S. patent that issued from the related Application Serial No. 09/477,924. As amended, the specification includes the serial number of the U.S. patent that issued from Application Serial No. 09/477,924. Accordingly, Applicants believe the objection to the specification to be overcome.

**The Objections to the Title**

The title was objected to as allegedly being not descriptive. As amended, the title describes the invention as relating to methods for treating manifestations of dysregulation of the GH/IGF axis by administration of an IGF-I variant. Applicants respectfully submit that the title is descriptive of the claimed invention. Accordingly, Applicants believe the objection to the title to be overcome.

**The Objections to Claim 4**

Claim 4 stands objected to as including numerous spaces before the term "chronic." As amended, these spaces are removed. Accordingly, Applicants believe the objection to Claim 4 to be overcome.

## CONCLUSION

For the reasons set forth above, Applicants believe that all claims are in condition for allowance. The Examiner is respectfully requested to reconsider the objections to the title, the specification, and to Claim 4, and to reconsider the rejections to Claims 1-7 in view of the above-mentioned amendments and arguments. Should the Examiner believe that a telephone interview would expedite the prosecution of this application, Applicants invite the Examiner to call the undersigned attorney at the telephone number indicated below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** referring to Attorney's Docket No. **39766-0131 R1-1D1**.

Respectfully submitted,

Dated: October 15, 2003 By: _____
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